Acute Kidney Injury Increases Mortality After Lung Transplantation

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Background. **Acute kidney injury requiring renal replacement therapy (RRT) is associated with increased mortality after cardiac surgery. Studies examining the impact of RRT after lung transplantation (LTx) are limited. We evaluated risk factors and outcomes associated with RRT after LTx.**

Methods. **We retrospectively reviewed all LTx recipients in the United Network for Organ Sharing database. Preoperative renal function was stratified by glomerular filtration rate (GFR) as determined by the Modification of Diet in Renal Disease formula (strata: ≥90, 60 to 90, and <60 mL · min^{-1}· 1.73m^{-2}). Primary outcomes were 30-day, 1-year, and 5-year survival and need for post-LTx RRT. Risk adjusted multivariable Cox proportional hazards regression examined mortality. A multivariable logistic regression model evaluated risk factors for RRT.**

Results. **From 2001 to 2011, 12,108 patients underwent LTx. After LTx, 655 patients (5.51%) required RRT. Patients requiring post-LTx RRT had decreased survival at 30 days (96.7% versus 76.0%, $p < 0.001$), 1 year (85.5% versus 35.8%, $p < 0.001$), and 5 years (56.4% versus 20.0%, $p < 0.001$). These differences persisted on multivariable analysis at 30 days (hazard ratio [HR] 7.98 [6.16 to 10.33], $p < 0.001$), 1 year (HR 7.93 [6.84 to 9.19], $p < 0.001$), and 5 years (HR 5.39 [4.75 to 6.11], $p < 0.001$). Preoperative kidney function was an important predictor of post-LTx RRT for a GFR of 60 to 90 (odds ratio 1.42 [1.16 to 1.75], $p = 0.001$) and a GFR less than 60 (odds ratio 2.68 [2.07 to 3.46], $p < 0.001$]. High center volume was protective.**

Conclusions. **In the largest study to evaluate acute kidney injury after LTx, the incidence of RRT is 5.51%. The need for post-LTx RRT dramatically increases both short- and long-term mortality. Several variables, including preoperative renal function, are predictors of post-LTx RRT and could be used to identify transplant candidates at risk for acute kidney injury.**

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Acute kidney injury (AKI) is a common complication after lung transplantation (LTx), occurring in 25% to 62% of LTx recipients [1–5]. In 5% to16% of patients, AKI is severe enough to require renal replacement therapy (RRT) [2–6]. Both AKI and severe AKI necessitating RRT have been associated with significant morbidity and as much as a fourfold increase in mortality [4–7]. Although a limited number of studies have examined risk factors for AKI and the impact of this complication on LTx outcomes, few studies have focused specifically on RRT. Moreover, existing studies of RRT after LTx are limited to single institutional experiences consisting of relatively small sample sizes [4, 6]. The United Network for Organ Sharing (UNOS) database of all LTx in the United States offers a unique opportunity to evaluate the incidence, impact, and risk factors for RRT after LTx in a large cohort.

Material and Methods

Data Source

For this study, we utilized the UNOS database from the UNOS registry, an open cohort of all patients undergoing LTx in the United States. The Johns Hopkins Medicine Institutional Review Board approved this study.

Study Design

This study is a retrospective cohort design of all adults (aged 18 years or older) who underwent LTx from 2000 to 2010. Patients undergoing retransplantation, combined heart-lung transplants, multiorgan transplants, patients

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Abbreviations and Acronyms

AKI = acute kidney injury
CI = confidence interval
CMV = cytomegalovirus
COPD = chronic obstructive pulmonary disease
ECMO = extracorporeal membrane oxygenation
GFR = glomerular filtration rate
HR = hazard ratio
IPF = idiopathic pulmonary fibrosis
LAS = lung allocation score
LTx = lung transplantation
PPH = primary pulmonary hypertension
RIFLE = risk, injury, failure, loss, end stage
RRT = renal replacement therapy
UNOS = United Network for Organ Sharing

on preoperative RRT, and patients missing preoperative creatinine were excluded. Primary stratification was according to the perioperative need for post-LTx RRT. Subgroup analysis was performed to compare patients before and after the Lung Allocation Score (LAS) era.

Variables Examined and Outcomes Measured

We examined pertinent covariates in the data set, including recipient demographics and comorbidities, recipient hemodynamics and measures of acuity, donor demographics and comorbidities, and transplant variables.

Recipient preoperative glomerular filtration rate (GFR) was calculated according to the Modified Diet in Renal Disease equation [8] as follows:

$$\text{GFR} = 175 \times (\text{Creatinine}_{\text{serum}})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if black ethnicity})$$

Based on their GFR, recipients were stratified by renal function: stratum 1, GFR 90 mL · min^{-1} · 1.73m^{-2}or more; stratum 2, GFR 60 to 90 mL · min^{-1} · 1.73m^{-2}; and stratum 3, GFR less than 60 mL · min^{-1} · 1.73m^{-2}.

The primary endpoints were 30 day, 1-year, and 5-year mortality. Risk factors for RRT were evaluated.

Statistical Analysis

We compared patient baseline characteristics using the *t* test (continuous parametric variables), the Wilcoxon rank-sum test (continuous nonparametric variables), and the χ^2 or Fisher's exact test (categorical variables) as appropriate. Survival was estimated using the Kaplan-Meier method.

Multivariable Cox proportional hazards regression models were constructed to estimate the risk of death with censoring for death and loss to follow-up. A multivariable logistic regression model was constructed to determine risk factors for post-LTx RRT. To construct all multivariable models, independent covariates were first tested in univariate fashion. Variables associated with mortality on exploratory analysis ($p < 0.20$), those with biological plausibility, and those previously reported in the literature to be significant were incorporated in a forward and backward stepwise fashion into the multivariable model. The likelihood ratio test and Akaike's information criterion were utilized in a nested model approach to identify which model had the greatest explanatory power.

For all analyses, *p* less than 0.05 (2-tailed) was considered statistically significant. Mean values are displayed with their standard deviations and median values are displayed with their interquartile ranges. Hazard ratios (HR) and odds ratios are presented with their 95% confidence intervals (CI). Statistical analysis was performed using STATA 11.2 (StataCorp LP, College Station, TX).

Results

Cohort Statistics

From 2001 to 2010, 13,499 patients receiving a LTx were included in the UNOS database. After excluding pediatric patients (n = 533), redo LTx (n = 497), multiorgan transplants (n = 34), patients requiring preoperative RRT (n = 9), and patients missing preoperative creatinine (n = 318), the final cohort comprised 12,108 patients.

The mean age of the entire cohort was 52 ± 13 years, and 6,657 (55.0%) were male. By strata, 5,273 recipients (43.6%) had a GFR 90 or more, 5,476 recipients (45.2%) had a GFR of 60 to 90, and 1,359 recipients (11.2%) had a GFR less than 60 mL · min^{-1} · 1.73m^{-2}. The most common indication for LTx was chronic obstructive pulmonary disease (COPD [n = 4,227; 34.9%]) followed by idiopathic pulmonary fibrosis (IPF [n = 3,369; 27.8%]). In the 6,835 patients transplanted in the post-LAS era, the mean LAS was 43.7 ± 14.7. Overall, 655 patients (5.51%) required post-LTx RRT.

Baseline Characteristics

An analysis of baseline characteristics stratified by the need for post-LTx RRT revealed several differences (Table 1). Patients requiring post-LTx RRT were more likely to be female, more likely to have diabetes mellitus, had poorer renal function, and were less likely to have COPD but more likely to have primary pulmonary hypertension (PPH). The RRT cohort had higher mean pulmonary artery pressures, were more likely to be hospitalized, to require intensive care unit care, and to require ventilatory or extracorporeal membrane oxygenation (ECMO) support before LTx. These patients were also more likely to undergo a bilateral lung transplantation, had longer ischemic times, a higher LAS, and were more likely to undergo LTx at lower volume centers. Although there were other statistically significant baseline differences, the absolute differences were small and unlikely clinically relevant.

Of patients requiring RRT, patients in the post-LAS era were older (49 ± 13 years versus 52 ± 13, $p < 0.001$), more likely to have IPF (57 of 269 [21.2%] versus 109 of 386 [28.2%], $p = 0.04$), less likely to have PPH (30 of 269 [11.2%] versus 19 of 386 [4.9%], $p = 0.003$), more likely to require ventilatory support (6 of 269 [2.2%] versus 48 of 386 [12.4%], $p < 0.001$) and ECMO support (1 of 269 [0.4%]